BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problems Mailbox.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 039 981**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification : 03.08.83

(51) Int. Cl.³ : C 07 H 15/08

(21) Application number : 81200505.6

(22) Date of filing : 11.05.81

(54) **Lactitol monohydrate and a method for the production of crystalline lactitol.**

(30) Priority : 14.05.80 NL 8002823

(43) Date of publication of application : 18.11.81 Bulletin 81/46

(45) Publication of the grant of the patent : 03.08.83 Bulletin 83/31

(84) Designated contracting states : AT BE CH DE FR GB IT LI LU NL SE

(56) References cited :
COMPTES RENDUS, 1920, 170, M.J.D. SENDERENS « Hydrogénation catalytique du lactose », pages 47-50
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, February 20, 1952, vol. 74, M.L. Wolfrom et al. « Lactitol Dihydrate »
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, March 1938 vol. 60 M.L. WOLFROM et al. « Crystalline lactositol », pages 571-573
CHEMICAL ABSTRACTS, vol. 90, 1979 page 391, abstract 37738f Columbus, Ohio, USA T. SAIJONMAA et al. « Lactitolsmilk sugar alcohols »

(73) Proprietor : C.V. CHEMIE COMBINATIE AMSTERDAM C.C.A.
Arkelsedijk 46 P.O. Box 21
NL-4200 AA Gorinchem (NL)

(72) Inventor : Wijnman, Christiaan Frederik
Fintstraat 2
NL-4285 XS Woudrichem (NL)
Inventor : van Velthuijsen, John Adriaan
H.M. van Randwijksingel 2
NL-4205 JS Gorinchem (NL)
Inventor : van den Berg, Hendrik
Mussenlaan 25
NL-4214 EG Vuren (NL)

(74) Representative : van der Beek, George Frans et al
Nederlandsch Octrooibureau Johan de Wittlaan 15
P.O. Box 29720
NL 2502 LS Den Haag (NL)

EP 0 039 981 B1

Lactitol monohydrate and a method for the production of crystalline lactitol

The invention relates to a method for the production of lactitol monohydrate and to a method for the production of crystalline lactitol by crystallization from an aqueous solution of lactitol.

Lactitol is lactose the glucose portion of which has been hydrogenated to sorbitol. Lactitol has the systematical name 4-β-D-galactopyranosyl-D-sorbitol.

The preparation of lactitol is of general knowledge. As described in « Agricultural and Food Chemistry », July-August 1979, *27*, 680-686 a 30-40 percent by weight lactose solution (based on the sum total) is normally used as the starting material such solution being hydrogenated at 100 °C and under a hydrogen pressure of 40 atmospheres in the presence of Raney-nickel. Upon the sedimentation of the catalyst the hydrogenated solution is filtered and purified by means of ion-exchangers and activated carbon.

The relative sweetness of lactitol amounts to 36 % when compared with the sweetness of a 5 % saccharose solution. It thus is clearly less sweet than sorbitol (relative sweetness of 55 %) and xylitol (relative sweetness of 96 %) (vide « Agricultural and Food Chemistry », July-August 1979, *27*, 680-686).

As reported in a German Patent (Maizena, 1974) the hydrolysis of lactitol by α-glucosidase (maltase) is much slower than that of lactose and maltose.

Whereas lactose is hydrolyzed completely by β-galactosidase within 45 minutes lactitol is only hydrolyzed for 10-15 % within the same period of time. Hence lactitol will only be decomposed to a minor degree in the alimentary track so that it is suitable as a replacement for sugar in products to be used by diabetics.

Lactitol is also suitable for use in low-caloric foods.

Lactitol is less hygroscopic than sorbitol, glycerol and xylitol and may consequently be used in the preparation of certain bakery products for diabetics such as light biscuits (Dutch patent Application 78.11204). Lactitol may therefore also be used in moisture insensitive coatings for chewing gum, gellies, fondant etc.

Furthermore lactitol possesses properties in view of which it is also well suited for several applications.

Due to the absence of a carbonyl group lactitol exibits a good stability against the exposure to head and to alkali. Heating an aqueous solution of 10 percent by weight of lactitol adjusted to a pH-value of 13 with NaOH (1 hour at 100 °C) does not produce any discoloration whereas a lactose solution when heated under the same conditions shows a strong discoloration.

The stability of lactitol in acidic medium is comparable to that of lactose. After heating solutions of 10 percent by weight of lactitol adjusted to a pH-value of 1 and 2, respectively, with HCl (4 hours at 100 °C) it appeared that 5.1 % and 1.4 % respectively, of the lactitol was hydrolyzed. Lactose solutions appear to be hydrolyzed for 5.4 % and 1.3 %, respectively, when heated under the same conditions.

Heating at higher temperatures (170-240 °C) caused anhydrisation of lactitol (production of lactitan).

Lactitol is soluble in water, dimethylsulfoxide and dimethylformamide and is miscible with other polyols (sorbitol, glycerol). It is slightly soluble in ethanol and diethylether.

Notwithstanding the fact that recent literature (Saijonmaa, T., Heikonen, M., Linko, P., Milchwissenschaft *33* (1978) 733-736, Schlweck, H., Süsswaren *14* (1978) 13-21) considers lactitol to be a substance that may be crystallized only with difficulty or not at all, nevertheless there are also reports to be found in the literature referring to a crystalline dihydrate (Wolfrom, M. L., Hann, Raymond M., Hudson, C.S., J. Am. Chem. Soc. *74* (1952) 1105) as well as to crystalline anhydrous lactitol.

Crystalline anhydrous lactitol has been obtained by the repeated extraction of a concentrated aqueous lactitol solution with absolute ethanol (removal of water). The amorphous hyroscopic mass thus obtained was combined with absolute ethanol whereby lactitol.0 aq crystallized in a yield of 80 % in a period of about one month.

Upon recrystallisation (dissolution in little water and addition of the same volume of ethanol) there were obtained small tetrahedric crystals having a melting point of 146 °C and a specific rotation of + 14°. Heating these crystals at 140 °C under reduced pressure above P_2O_5 for a period of 54 hours caused almost no loss of weight.

Lactitol dihydrate possesses a melting point of 76-78 °C and was presumably first described by Senderens, J. B., Compt. Rend. 170 (1920) 47-50. This investigator evaporated a hydrogenated lactose solution on a water bath until a syrupy mass was obtained, which mass kept at room temperature started to crystallize after some days ; the product showed a melting point of 78 °C and specific rotation of + 12.2°.

Since drying the crystals at 130 °C to a constant weight caused a weight loss of 5 % (water) Senderens thought he had obtained the monohydrate.

It has now become apparent that when drying lactitol dihydrate at 130 °C for three days there will be a loss of weight of only 5 %.

The publication by Senderens does not disclose any determination of the moisture content according to the Karl Fischer method ; such a determination would presumably have yielded a higher water content corresponding to the dihydrate (containing about 9.5 percent by weight of water).

Also in view of the low melting point (78 °C) it may thus be assumed that at that time Senderens had recovered the dihydrate instead of the monohydrate (the melting point indicated by him is 78 °C, whereas lactitol monohydrate has a melting point of 121-123 °C and the dihydrate has a melting point of 76-78 °C).

Wolfrom, M. L. Hann, Raymond M., Hudson, C. S., (J. Am. Chem. Soc. *74* (1952) 1105) have also obtained the dihydrate and confirmed the composition thereof on the basis of the elementary analysis. They found a melting point of 72.5-74 °C and a specific rotation of + 11.5°.

Van Velthuijsen in Agriculture and Food Chemistry *27* (1979) 680-686 describes an impure lactitol monohydrate which contains 3 % mannitol, 0.5 % sorbitol, 0.5 % dulcitol and 0.5 % lower polyols. The melting point of this substance is 94-97 °C.

According to the invention there has now been found a crystalline lactitol monohydrate Formula $C_{12}H_{24}O_{11} \cdot H_2O$; melting point 121-123 °C; crystal system orthorhombic; dimensions of unit cell a = 7.908 Å, b = 12.685 Å, c = 15.931 Å; space group P 2, 2, 2; 4 molecules per unit cell having a volume 1 577.9 Å^3, as well as a method for the production of crystalline lactitol by crystallization from an aqueous solution of lactitol by means of which lactitol monohydrate as well as lactitol dihydrate may be produced on an industrial scale, said method being characterized by

a) seeding an aqueous solution of from 70 to 85 percent by weight, preferably from 78 to 82 percent by weight, of lactitol with lactitol monohydrate at from 45 °C to 55 °C and causing lactitol monohydrate to crystallize at from 40 °C to 50 °C, preferably between 43 °C and 47 °C, said lactitol monohydrate optionally being recovered,

b) optionally subsequently cooling the mother liquor to from 15 °C to 25 °C, preferably to from 18 °C to 22 °C, seeding the same with crystalline lactitol monohydrate seeds and causing the lactitol monohydrate to crystallize at this temperature, said lactitol monohydrate optionally being recovered,

c) optionally causing the mother liquor obtained under b) to crystallize further at from 10 °C to 25 °C, preferably at from [illegible] to 20 °C and recovering lactitol dihydrate, or

d) seeding an aqueous solution of from 67 to 76 percent by weight, preferably of from 68 to 76 percent by weight, in particular of from 72 to 74 percent by weight, of lactitol with crystalline lactitol dihydrate seeds and causing lactitol dihydrate to crystallize and recovering the same.

The aqueous solution of lactitol may be prepared in an appropriate way by the hydrogenation of a lactose solution. By way of example there may be provided a solution of 1 500 kg lactose dissolved in 2 200 liter demineralized water at 60 °C. The solution is heated to 100 °C and pressurized with hydrogen to a hydrogen pressure of 40 atmospheres to which there is added 100 kg Raney-nickel as a catalyst. Upon completion of the hydrogenation the solution thus obtained is passed over ion exchangers for the removal of nickel ions and organic acids formed. After completing this treatment the solution shows a pH-value of 7.5 and a conductivity of 1.3 micro siemens (at 20-25 °C) and a refractometer determined density of 30° Brix.

The measurement was carried out by means of a refractometer provided with a so-called sugar or Brix scale. This graduation is based on the percentage by weight of saccharose in a solution. For other sugars the same scale is used is an indication for the concentration (vide also Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition Vol. 19 pages 158 and 159).

From the purified lactitol solution there may be recovered also crystalline lactitol dihydrate upon concentrating said solution provided the crystallization is performed at 10-37 °C and the solution is first seeded with crystalline lactitol dihydrate seeds. The dihydrate may also be obtained from the concentrated solution without seeding in course of time (vide example I). The crystallization may then be induced by a method known per se, such as scraping the walls of the crystallization vessel.

Lactitol monohydrate may be prepared very advantageously by seeding an aqueous solution of from 75 to 85 percent by weight of lactitol with lactitol monohydrate at 45-55 °C and then causing the solution to crystallize at 40-50 °C. Thereby the lactitol monohydrate may be recovered in a crystallization yield of 40-60 %. It is of particular advantage to seed the resulting mother liquor at 15-25 °C with lactitol monohydrate and to cause the same to crystallize at this temperature. Thereby a crystallization yield of yet 20-25 % is obtained.

Furthermore lactitol monohydrate may be produced by mixing 1 part by weight of an aqueous lactitol solution having a concentration of from 60 to 75 percent by weight with from 1 to 3 parts by weight of methanol or ethanol and subsequently cooling the mixture to 15-25 °C while agitating. Thereby lactitol monohydrate crystallizes. It is of advantage therein to use 1 part by weight of a lactitol solution having a concentration of from 65-70 percent by weight and to mix the same with from 1 to 2 parts by weight of methanol or ethanol. In particular one will use 1 part by weight of the lactitol solution and will mix the same with 1 part by weight of ethanol whereupon one will allow the solution to cool to 18-22 °C while agitating and then recover the crystallized lactitol monohydrate.

In particular it is very advantageous to mix 1 part by weight of a lactitol solution having a concentration of 70 percent by weight with 1 part by weight of ethanol at 60 °C and then to cool the mixture to 25 °C while agitating whereupon the lactitol monohydrate crystallizes.

A X-ray diffraction analysis has been performed on a single crystal of lactitol dihydrate in order to determine the crystal structure thereof. This analysis shows that the dihydrate crystal belongs to the tetragonal crystal system and that unit cell comprises 8 lactitol molecules and 16 water molecules. The second water molecule is lodged within the space between the sorbitol chain and the galactopyranosyl

ring as will be apparent from the projection formula (Fig. 1). The dimensions of the unit cell are : a = b = 8.762 Å, c = 45.508 Å ; hence this unit cell is indeed very elongated. The space group is $P4_32_12$, the cell volume is 3 493.8 Å^3 and the calculated density of the crystal is 1.445 g/cm^3.

A single crystal of lactitol dihydrate has now been prepared for the first time. The lactitol dihydrate known previously was of insufficient purity for the preparation of a single crystal. Thereby it became now possible to perform a X-ray diffraction analysis (vide Table A).

Table A

	Lactitol monohydrate	Lactitol dihydrate
Formula	$C_{12}H_{24}O_{11} \cdot H_2O$	$C_{12}H_{24}O_{11} \cdot 2H_2O$
Crystal system	orthorhombic	tetragonal
Dimensions of the unit cell	a = 7.808(2) Å b = 12.685(2) Å c = 15.931(3) Å	a = b = 8.762(2) Å c = 45.508(10) Å
systematic extinctions	h00, h = 2n + 1 0k0, k = 2n + 1 001, l = 2n + 1	h00, h = 2n + 1 0k0, k = 2n + 1 001, l = 4n + 1
Space group	$P2_12_12_1$	$P4_32_12$
Number of molecules per unit cell	4	8
Unit cell volume.	1 577.9 Å^3	3 493.8 Å^3
Density (calculated)	1.523 g · cm^{-3}	1.445 g · cm^{-3}
Number of reflections measured	2 061	2 458
Number of reflections observed	1 781	2 091
Number of parameters	296	311
Reliability index (full matrix least squares)	0.032	0.041

Lactitol monohydrate

A part from the dihydrate there has now been found also a new type of crystal containing only one molecule of crystal water, thus a monohydrate. It is true that in Agricultural and Food Chemistry Van Velthuysen describes a compound indicated to be lactitol monohydrate but this product is impure. It contains mannitol, sorbitol, dulcitol and lower polyols as stated before and has a melting point of 94-97 °C, whereas the newly found product is pure and has a melting point of 121-123 °C. The solubility differs also. The solubility of the pure monohydrate in water at room temperature is less (56 %) than that of the impure product (64 %).

Lactitol monohydrate shows when heated at 130 °C for three days contrary to lactitol dihydrate a loss of weight of 2 %.

It has now been found that pure lactitol monohydrate may be produced by crystallization of lactitol from an alcoholic medium.

It has also been found that lactitol monohydrate may be obtained by crystallization of an aqueous solution of lactitol at temperatures between 10 °C and 50 °C when the solution is seeded under proper conditions with crystalline lactitol monohydrate seeds obtained from an alcoholic medium.

Surprisingly it appears to be possible to obtain the monohydrate by a first crystallization whereupon lactitol dihydrate crystallizes from the mother liquor. Thus is illustrated in example XI.

A single crystal of lactitol monohydrate obtained from an ethanol-water medium has likewise been subjected to a X-ray diffraction analysis in order to determine the crystal structure thereof. From this analysis it has become apparent that the monohydrate crystal belongs to the rhombic crystal system and that the unit cell contains 4 lactitol molecules and 4 water molecules. The dimensions of the unit cell are : a = 7.808 Å, b = 12.685 Å and c = 15.931 Å. The space group is $P2_12_12_1$, the unit cell volume is 1577.9 Å^3 and the calculated density of the crystals is 1.523 g/cm^3. The structure has been represented in Fig. 2 (vide also Table A). This structure likewise holds for lactitol monohydrate obtained by crystallization from an aqueous medium. The similarity between both forms of crystal is apparent from the fact that they yield identical powder diagrams and show a similar melting point behaviour when determined with the aid of differential-scanning calorimetry.

Example 1

A lactitol solution purified by passing over ion exchangers and having a refractive index of 30° Brix was concentrated under reduced pressure to an index of 75° Brix (dry solids content of 71.6 percent by weight). From this lactitol syrup 2 500 g were taken. Upon cooling to 18 °C crystals separated slowly from the syrup which crystals were removed from the mother liquor by centrifuging and then dried at 50 °C.

Yield : 1 190 g lactitol dihydrate or 60 % based on 1 791 g dry solids. Melting point : 79-80 °C ; moisture content (Karl Fischer) : 9.7 percent by weight. The mother liquor had a refractive index of 58° Brix (dry solids content of 55.4 percent by weight).

Examples II-V

The crystallization conditions are not limited to those mentioned in example I. It appears to be possible to recover crystalline lactitol dihydrate from lactitol solutions having different lactitol concentrations. In each instance an amount of 1 600 g lactitol dihydrate was dissolved to that effect in 930 g, 730 g, 550 g and 400 g water, respectively. Upon cooling to 25 °C each one of the solutions was seeded with 16 g ground lactitol dihydrate followed by further cooling to 15 °C. After 24 hours the crystals produced were separated from the mother liquor by centrifuging whereupon the crystals were washed with 50 ml water in the centrifuge and dried at a temperature of 50 °C. In Tabel B the results thus obtained are summarized. The crystallization yields indicated in percent include the 1 percent by weight of crystal seeds.

From the results summarized in Table B is may be concluded that an increase of the initial lactitol concentration increases the crystallization yield at the same lactitol content in the mother liquor. At an initial concentration of less than 57 percent by weight of lactitol the crystallization yield will become less than 30 % i. e. too low for the application on an industrial scale. At an initial concentration of more than 72 percent by weight a thick crystal slurry is formed which cannot be worked up anymore on an industrial scale.

Table B

Example	Lactitol dihydrate (g)	Water (g)	Lactitol product (% by wt)	Lactitol product (g)	Melting point (°C)	Water content (%)	Mother liquor (g)	Mother liquor (bx)	Cryst yield (%)
I	1 600	930	57	480	80-81	10.9	1 857	54	30.0
III	1 600	730	62	776	80-81	10.8	1 329	54	42.5
IV	1 600	550	67	987	80-81	10.7	945	54	61,7
V	1 600	400	72	1 040	78-80	10.7	821	55	65.0

Example VI

225 g water was added to 760 g lactitol dihydrate whereupon the mixture was heated to 100 °C while agitating whereby a clear 70 percent by weight lactitol solution was obtained. Upon cooling to 60 °C 1.3 l ethanol (96 %) was added in small increments while agitating and keeping the temperature at 60 °C. Upon cooling to 45 °C lactitol started to crystallize. After continued cooling to room temperature while agitating the product was recovered on a suction filter and dried at 50 °C in a drying cabinet. The yield of lactitol monohydrate was 684 g or 94 % based on the lactitol used, melting point : 121-123 °C ; moisture content : 5.8 percent by weight (Karl Fischer).

Examples VII-X

Crystalline lactitol monohydrate was prepared from aqueous lactitol solutions having different lactitol contents varying from 70 to 80 percent by weight. Thereby in each instance an amount of 1 700 g lactitol dihydrate was dissolved in 490 g, 350 g, 300 g and 230 g water, respectively, at a temperature of 100 °C. Upon cooling to 50 °C the solution was seeded with 15 g ground lactitol monohydrate whereupon the cooling was continued to 45 °C. After a crystallization for 24 hours at 45 °C the crystals were separated from the mother liquor in a laboratory centrifuge, washed with 50 ml water in the centrifuge and dried at 50 °C in a drying cabinet. Thereupon the mother liquors were also seeded with monohydrate crystals. After a crystallization for 24 hours at 15 °C the monohydrate crystals formed were separated by centrifuging, washed with 25 ml water and dried at 50 °C. The results thus obtained are compiled in Table C.

(See the Table C. page 6)

Table C

Example	Lactitol used (% by wt)	Product (g)	Melting point (°C)	Crystal water content (% by wt)	Crystallization yield (%)	Ibid total (°C)	Mother liquor (g)	Mother liquor (bx)
VII	70	310	115-120	5.3	19	59	1 628	70.5
		655	118-121	5.2	40		850	54
VIII	75	666	118-120	5.2	41	65	1 101	71
		395	123	5.1	24		609	54
IX	77	740	115-120	5.4	45	68	1 059	71
		372	123	5.3	23		598	54
X	80	912	110-120	5.4	56	77	844	71
		341	123	5.6	21		341	54

From these tests it is apparent that an increase of the lactitol concentration from 70 percent by weight to 80 percent by weight causes the crystallization yield of the first crystallization to increase strongly whereas contrary thereto the yield of the second crystallization however decreases. The total crystallization yield however rises when increasing the lactitol concentration to almost 80 %. From the mother liquors of the first crystallization pure monohydrate is crystallized again.

Example XI

500 g water were added to 3 800 g lactitol dihydrate and the mixture was heated to 100 °C whereby a clear 80 percent by weight lactitol solution was obtained. Upon cooling to 45 °C the solution was seeded with 36 g ground lactitol monohydrate resulting in the crystallization of the solution accompanied by generating of heat (a rise in temperature from 45 °C to 55 °C occurred).

After a crystallization for 24 hours at 45 °C the crystals were separated from the mother liquor in a laboratory centrifuge; after removal of the mother liquor by centrifuging the product was washed with 100 ml water in total in the centrifuge. The yield of the product dried at 50 °C was 2 010 g lactitol monohydrate or 55 % based on the lactitol used. The melting point of the product was 121-123 °C and the moisture content was 5.2 percent by weight.

The mother liquor (1 910 g of 76.5° Brix) was seeded with 15 g ground lactitol dihydrate and subsequently cooled to 15 °C. After a crystallization for 24 hours at 15 °C the crystals were removed by centrifuging and washed with 40 ml water in the centrifuge.

The yield of lactitol dihydrate dried at 50 °C was 810 g or 21 % based on the lactitol used. The melting point was 78-79 °C and the moisture content was 9.7 percent by weight. Accordingly the total crystallization yield was 55 % + 21 % = 76 %.

The final mother liquor obtained amounted to 1 060 g of 59 °C Brix (dry solids content of 58 percent by weight).

Examples XII-XXVII

Examples XII-XXVII elucidate the conditions at which lactitol monohydrate and lactitol dihydrate, respectively, may be obtained from aqueous solutions of lactitol. In each instance 200 g lactitol dihydrate was used as the starting material which was dissolved in an amount of water varying from 40 g to 50 g at 100 °C. Thereupon the solutions obtained were cooled to a temperature varying from 25 °C to 45 °C and seeded with 2 g monohydrate or 2 g dihydrate. The crystallization proper occurred at temperatures between 18 °C and 45 °C.

The obtained crystals were separated from the mother liquor in a small model laboratory centrifuge, washed with 5 ml water in the centrifuge and dried at 50 °C. The melting point of each fraction of crystalline lactitol was determined.

In Table D (examples XII to XXI, inclusive) the results are compiled which were obtained when the crystallization temperature was kept at the seeding temperature. It appears in general that upon seeding with monohydrate there is again formed the monohydrate whereas seeding with dihydrate yields again dihydrate. The test performed at 45 °C however is an exception in that solely the monohydrate was formed. At this temperature (and presumably also at yet higher temperatures) the monohydrate is apparently the sole stable modification.

(See the Table D, page 7)

[illegible] = 118-125

Table D

Example	Lactitol dihydrate (g)	Water (g)	Lactitol (% by wt)	Seeding temp. (°C)	Seeds	Produkt (g)	Melting point (°C)	Crystals	Mother liquor (bx)
XII	200	40	75.4	45	mono	77	121-123	mono	68
XIII	200	40	75.4	45	di	68	115-123	mono	68
XIV	200	45	73.9	37	mono	63	122-123	mono	67
XV	200	45	73.9	37	di	100	81-83	di	65
XVI	200	45	73.9	35	mono	78	122-124	mono	65
XVII	200	45	73.9	35	di	112	81-83	di	63
XVIII	200	45	73.9	32	mono	78	122-123	mono	59
XIX	200	45	73.9	32	di	106	81-83	di	61
XX	200	48	73.0	25	mono	66	121-123	mono	58
XXI	200	48	73.0	25	di	119	80-82	di	54

Table E

Example	Lactitol dihydrate (g)	Water (g)	Lactitol (% by wt)	Seeding temp. (°C)	Seeds	Cryst. temp. (°C)	Product (g)	Melting point (°C)	Crystals	Mother liquor (bx)
XXII	200	42	74.8	45	mono	18	106	121-123	mono	58
XXIIII	200	42	74.8	45	di	18	132	81-83	di	54
XXIV	200	50	72.4	37	mono	18	96	123-125	mono	54
XXV	200	50	72.4	37	di	18	126	80-82	di	54
XXVI	200	50	72.4	25	mono	18	99	122-124	mono	54
XXVII	200	50	72.4	25	di	18	124	81-83	di	54

The results compiled in Table E (examples XXII to XXVII, inclusive) were obtained at one and the same crystallization temperature (18 °C) whereas the seeding temperature varied from 45 °C to 25 °C. It appears that seeding with the monohydrate again yields the monohydrate and seeding with the dihydrate again yields the dihydrate. The difference in comparison with example XIII consists therein that if a seeding with the dihydrate performed at 45 °C is followed by a crystallization at 18 °C (example XXIII) there is now produced the dihydrate instead of the monohydrate like in example XIII. Due to the rapid cooling from 45 °C to 18 °C the seeding material did apparently not have the opportunity to convert from the dihydrate form to the monohydrate form.

A blended sample was made of all the monohydrate products obtained by the tests of examples XII to XXVII, inclusive, which sample was analyzed with respect to the moisture content in accordance with the Karl Fischer method ; the moisture content was found to be 5.2 percent by weight. The blended sample of the dihydrates was found to have a moisture content of 10.0 percent by weight.

Example XXVIII

960 g lactitol dihydrate (860 g anhydric lactitol) were dissolved in 125 g water at 100 °C. Upon cooling to 50 °C the 80 percent by weight lactitol solution was seeded with 9.5 g ground dihydrate (1 percent by weight based on the lactitol dissolved). After crystallization for 48 hours at 45 °C the crystals formed were separated from the mother liquour in a laboratory centrifuge, washed with 25 ml water and dried at 45 °C (drying cabinet). There were then obtained 440 g lactitol monohydrate (melting point : 118-120 °C ; moisture content : 4.9 %) or 49 % based on the lactitol used.

After a crystallization for 24 hours at 18 °C there could be recovered from the mother liquor seeded with 4 g ground dihydrate a further crop of 240 g lactitol dihydrate (meltingpoint : 80-82 °C ; moisture content : 10.0 %) or 25 % based on the lactitol used.

The total crystallization yield thus amounted to 49 % + 25 % = 74 %.

Example XXIX

This example illustrates the direct production of lactitol monohydrate from a purified and concentrated hydrogenated lactose solution.

2 500 g purified concentrated lactitol syrup (80° Brix, 76.4 percent by weight of dry solids) were seeded with 15 g ground lactitol monohydrate at 45 °C. After a crystallization for 48 hours at 45 °C the crystals were separated from the mother liquor in a laboratory centrifuge, washed with 50 ml water and dried at 45 °C (drying cabinet). Yield : 875 g monohydrate or 43.5 percent by weight based on the dry solids content of the lactitol syrup ; melting point 110-120 °C ; moisture content : 5.7 percent by weight.

Upon seeding with about 5 g ground monohydrate there was yet crystallized from the mother liquor a further crop 446 g lactitol monohydrate or 22.2 percent by weight based on the dry solids content ; melting point : 115-120 °C ; moisture content : 5.5 percent by weight.

After about 1 week at 18-20 °C there was crystallized from the second mother liquor yet 202 g lactitol dihydrate of 9.6 percent by weight based on the dry solid content ; melting point : 82-84 °C ; moisture content : 9.8 percent by weight.

The total crystallization yield thus amounted to 75.3 % including 1 % of seeding crystals.

The final mother liquor yet showed a refractive index of 57° Brix (dry solids content of 54 percent by weight).

Example XXX

The hydrogenated lactose solution described in example XXIX was used as the starting material. This solution was concentrated to 75° Brix (dry solids content of 72 percent by weight). The solution was seeded with lactitol dihydrate at room temperature. Hereby only the lactitol dihydrate crystallized. The crystallization yield was 60 %.

Claims

1. Crystalline lactitol monohydrate of the formula $C_{12}H_{24}O_{11} \cdot H_2O$; melting point 121-123 °C ; crystal system orthorhombic ; dimensions of unit cell a = 7.808 Å, b = 12.685 Å, c = 15.931 Å ; space group p 2,2,2 ; 4 molecules per unit cell having a volume of 1 577.9 Å^3.

2. A method for the production of crystalline lactitol by crystallization from an aqueous solution of lactitol characterized by

a) seeding an aqueous solution of from 70 to 85 percent by weight of lactitol with lactitol monohydrate at from 45 °C to 55 °C and causing lactitol monohydrate to crystallize at from 40 °C to 50 °C, preferably between 43 °C and 47 °C, said lactitol monohydrate optionally being recovered,

b) optionally subsequently cooling the mother liquor to from 15 °C to 25 °C, seeding the same with crystalline lactitol monohydrate seeds and causing the lactitol monohydrate to crystallize at this temperature, said lactitol monohydrate optionally being recovered,

c) optionally causing the mother liquor obtained under b) to crystallize further at from 10 °C to 25 °C and recovering lactitol dihydrate, or

d) seeding an aqueous solution of from 57 to 76 percent by weight of lactitol with crystalline lactitol dihydrate seeds and causing lactitol dihydrate to crystallize and recovering the same.

3. The method according to claim 2a, characterized by starting from a solution of from 78 to 82 percent by weight of lactitol.

4. The method according to claim 2a, characterized by causing lactitol monohydrate to crystallize at from 43 °C to 47 °C.

5. The method according to claim 2b, characterized by causing the mother liquor to cool to from 18 °C to 22 °C and thereupon seeding the same with crystalline lactitol monohydrate seeds.

6. The method according to claim 2b, characterized by causing lactitol monohydrate to crystallize at from 18 °C to 22 °C.

7. The method according to claim 2c, characterized by causing lactitol dihydrate to crystallize at from 15 °C to 20 °C.

8. The method according to claim 2d, characterized by recovering lactitol dihydrate from a solution of from 68 to 76 percent by weight of lactitol.

9. The method according to claim 8, characterized by utilizing a solution of from 72 to 74 percent by weight of lactitol.

10. The method according, to claim 2d, characterized by causing lactitol dihydrate to crystallize at from 15 °C to 20 °C.

11. The method according to claim 2, characterized by starting from a lactitol solution obtained by the hydrogenation of a lactose solution.

12. A method for the production of crystalline lactitol monohydrate characterized by seeding an aqueous solution of from 78 to 82 percent by weight of lactitol with lactitol monohydrate at from 45 °C to 55 °C and thereupon causing said solution to crystallize at from 40 °C to 50 °C and recovering the lactitol monohydrate.

13. The method according to claim 12, characterized by seeding the mother liquor thus obtained with lactitol monohydrate at from 15 °C to 25 °C and then causing the mother liquor to crystallize at this temperature and recovering the lactitol monohydrate.

14. A method for the production of lactitol monohydrate according to claim 1, characterized by mixing 1 part by weight of an aqueous lactitol solution having a concentration of from 60 to 75 percent by weight with from 1 to 3 parts by weight of methanol or ethanol and thereupon causing the mixture to cool to from 15 °C to 25 °C while agitating and recovering the crystallizing lactitol monohydrate.

15. The method according to claim 14, characterized by mixing 1 part by weight of a lactitol solution having a concentration of from 65 to 70 percent by weight with from 1 to 2 parts by weight of methanol or ethanol.

16. The method according to claim 14, characterized by mixing 1 part by weight of the lactitol solution with 1 part by weight of ethanol and thereupon causing the mixture to cool to from 18 °C to 22 °C while agitating causing lactitol monohydrate to crystallize and recovering the same.

17. The method according to claim 14, characterized by mixing 1 part by weight of a lactitol solution having a concentration of 70 percent by weight with 1 part by weight of ethanol and thereupon causing the mixture to cool to 20 °C while agitating thus crystallizing lactitol monohydrate.

Ansprüche

1. Kristallines Laktitol-Monohydrat (Laktit-Monohydrat) der Formel $C_{12}H_{24}O_{11} \cdot H_2O$; Schmelzpunkt 121-123 °C; Kristallsystem ortorhombisch; Abmessungen der Einheitszelle a = 7,808 Å, b = 12,685 Å, c = 15,931 Å; Raumgruppe p 2,2,2; 4 Moleküle je Einheitszelle mit einem Volumen von 1 577,9 Å.

2. Ein Verfahren zur Herstellung von kristallinem Laktitol durch Kristallisation aus einer wäßrigen Laktitollösung, dadurch gekennzeichnet, daß man

a) eine wäßrige Lösung von 70 bis 85 Gewichtsprozent Laktitol mit Laktitol-Monohydrat bei 45 °C bis 55 °C beimpft und das Laktitol-Monohydrat bei 40 °C bis 50 °C, vorzugsweise zwischen 43 °C und 47 °C, zur Kristallisation bringt, das genannte Laktitol-Monohydrat gegebenenfalls gewinnt,

b) gegebenenfalls anschließend die Mutterlauge auf 15 °C bis 25 °C abkühlt, sie mit Keimen von kristallinem Laktitol-Monohydrat beimpft und das Laktitol-Monohydrat bei dieser Temperatur zur Kristallisation bringt, das genannte Laktitol-Monohydrat gegebenenfalls gewinnt,

c) gegebenenfalls die unter b) erhaltene Mutterlauge bei 10 °C bis 25 °C weiter kristallisieren läßt und Laktitol-Dihydrat gewinnt, oder

d) eine wäßrige Lösung von 57 bis 76 Gewichtsprozent Laktitol mit Keimen von kristallinem Laktitol-Dihydrat beimpft und das Laktitol-Dihydrat zur Kristallisation bringt und es gewinnt.

3. Das Verfahren gemäß Anspruch 2a, dadurch gekennzeichnet, daß man von einer Lösung von 78 bis 82 Gewichtsprozent Laktitol ausgeht.

4. Das Verfahren gemäß Anspruch 2a, dadurch gekennzeichnet, daß man Laktitol-Monohydrat bei 43 °C bis 47 °C zur Kristallisation bringt.

5. Das Verfahren gemäß Anspruch 2b, dadurch gekennzeichnet, daß man die Mutterlauge auf 18 bis 22 °C abkühlen läßt und sie anschließend mit Keimen von kristallinem Laktitol-Monohydrat beimpft.

6. Das Verfahren gemäß Anspruch 2b, dadurch gekennzeichnet, daß man Laktitol-Monohydrat bei 18 bis 22 °C zur Kristallisation bringt.

7. Das Verfahren gemäß Anspruch 2c, dadurch gekennzeichnet, daß man Laktitol-Dihydrat bei 15 °C bis 20 °C zur Kristallisation bringt.

8. Das Verfahren gemäß Anspruch 2d, dadurch gekennzeichnet, daß man Laktitol-Dihydrat aus einer Lösung von 68 bis 76 Gewichtsprozent Laktitol gewinnt.

9. Das Verfahren gemäß Anspruch 8, dadurch gekennzeichnet, daß man eine Lösung vom 72 bis 74 Gewichtsprozent Laktitol verwendet.

10. Das Verfahren gemäß Anspruch 2, dadurch gekennzeichnet, daß man Laktitol-Dihydrat bei 15 °C bis 20 °C zur Kristallisation bringt.

11. Das Verfahren gemäß Anspruch 2, dadurch gekennzeichnet, daß man von einer Laktitol-Lösung, die durch Hydrierung einer Laktoselösung erhalten wird, ausgeht.

12. Ein Verfahren zur Herstellung von kristallinem Laktitol-Monohydrat, dadurch gekennzeichnet, daß man eine wäßrige Lösung von 78 bis 82 Gewichtsprozent Laktitol mit Laktitol-Monohydrat bei 45 °C bis 55 °C beimpft und anschließend die Lösung bei 40 °C bis 50 °C kristallisieren läßt und das Laktitol-Monohydrat gewinnt.

13. Das Verfahren gemäß Anspruch 12, dadurch gekennzeichnet, daß man die so erhaltene Mutterlauge mit Laktitol-Monohydrat bei 15 °C bis 25 °C beimpft und die Mutterlauge bei dieser Temperatur kristallisieren läßt und das Laktitol-monohydrat gewinnt.

14. Ein Verfahren zur Herstellung von Laktitol-Monohydrat gemäß Anspruch 1, dadurch gekennzeichnet, daß man 1 Gewichtsteil einer wäßrigen Laktitollösung mit einer Konzentration von 60 bis 75 Gewichtsprozent mit 1 bis 3 Gewichtsteilen Methanol oder Äthanol vermischt und anschließend das Gemisch auf 15 °C bis 25 °C unter Bewegen abkühlen läßt und das kristalline Laktitol-Monohydrat gewinnt.

15. Das Verfahren gemäß Anspruch 14, dadurch gekennzeichnet, daß man 1 Gewichsteil Laktitollösung mit einer Konzentration von 65 bis 70 Gewichtsprozent mit 1 bis 2 Gewichtsteile Methanol oder Äthanol vermischt.

16. Das Verfahren gemäß Anspruch 14, dadurch gekennzeichnet, daß man 1 Gewichtsteil Laktitollösung mit 1 Gewichtsteil Äthanol vermischt und anschließend das Gemisch unter Bewegen auf 18 °C bis 22 °C abkühlen läßt, wodurch man das Laktitol-Monohydrat zur Kristallisation bringt und es gewinnt.

17. Das Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß man 1 Gewichtsteil einer Laktitollösung mit einer Konzentration von 70 Gewichtsprozent mit 1 Gewichtsteil Äthanol vermischt und anschließend das Gemisch auf 20 °C unter Bewegen abkühlen läßt, wodurch das Laktitol-Monohydrat kristallisiert.

Revendications

1. Monohydrate de lactitol cristallin de formule $C_{12}H_{24}O_{11} \cdot H_2O$; point de fusion 121 à 123 °C ; système cristallin orthorhombique ; dimensions de la maille élémentaire a = 7,808 Å, b = 12,685 Å, c = 15,931 Å ; groupe spatial p 2,2,2 ; 4 molécules par maille élémentaire, présentant un volume de 1 577,9 Å^3.

2. Procédé pour la production de lactitol cristallin par cristallisation à partir d'une solution aqueuse de lactitol, caractérisé par les opérations consistant :

a) à ensemencer une solution aqueuse à 70 à 85 pour cent en poids de lactitol avec du monohydrate de lactitol à une température comprise entre 45 et 55 °C et à faire cristalliser du monohydrate de lactitol à une température comprise entre 40 et 50 °C, et de préférence entre 43 et 47 °C, ledit monohydrate de lactitol étant éventuellement récupéré,

b) à éventuellement refroidir ensuite la liqueur mère à une température comprise entre 15 et 25 °C, à ensemencer celle-ci avec des germes cristallins de monohydrate de lactitol et à faire cristalliser le monohydrate de lactitol à cette température, ledit monohydrate de lactitol étant éventuellement récupéré,

c) à éventuellement poursuivre la cristallisation de la liqueur mère obtenue en b) à une température comprise entre 10 et 25 °C et à récupérer du dihydrate de lactitol, ou

d) à ensemencer une solution aqueuse à 57 à 78 pour cent en poids de lactitol avec des germes cristallins de dihydrate de lactitol et à faire cristalliser du dihydrate de lactitol et à récupérer celui-ci.

3. Procédé selon la revendication 2a, caractérisé en ce que l'on part d'une solution à 78 à 82 pour cent en poids de lactitol.

4. Procédé selon la revendication 2a, caractérisé en ce que l'on fait cristalliser du monohydrate de lactitol à une température comprise entre 43 et 47 °C.

5. Procédé selon la revendication 2b, caractérisé en ce que l'on fait refroidir la liqueur mère à une température comprise entre 18 et 22 °C et en ce que l'on ensemence alors celle-ci avec des germes cristallins de monohydrate de lactitol.

6. Procédé selon la revendication 2b, caractérisé en ce que l'on fait cristalliser du monohydrate de lactitol à une température comprise entre 18 et 22 °C.

7. Procédé selon la revendication 2c, caractérisé en ce que l'on fait cristalliser du dihydrate de lactitol à une température comprise entre 15 et 20 °C.

8. Procédé selon la revendication 2d, caractérisé en ce que l'on récupère du dihydrate de lactitol d'une solution à 68 à 78 pour cent en poids de lactitol.

9. Procédé selon la revendication 8, caractérisé par la mise en œuvre d'une solution à 72 à 74 pour cent en poids de lactitol.

10. Procédé selon la revendication 2d, caractérisé en ce que l'on fait cristalliser du dihydrate de lactitol à une température comprise entre 15 et 20 °C.

11. Procédé selon la revendication 2, caractérisé en ce que l'on part d'une solution de lactitol obtenue par l'hydrogénation d'une solution de lactose.

12. Procédé pour la production de monohydrate de lactitol cristallin, caractérisé en ce que l'on ensemence une solution aqueuse à 78 à 82 pour cent de lactitol avec du monohydrate de lactitol à une température comprise entre 45 et 55 °C et en ce que l'on fait alors cristalliser ladite solution à une température comprise entre 40 et 50 °C et en ce que l'on récupère le monohydrate de lactitol.

13. Procédé selon la revendication 12, caractérisé en ce que l'on ensemence la liqueur mère ainsi obtenue avec du monohydrate de lactitol à une température comprise entre 15 et 25 °C et en ce que l'on fait ensuite cristalliser la liqueur mère à cette température et en ce que l'on récupère le monohydrate de lactitol.

14. Procédé pour la production de monohydrate de lactitol selon la revendication 1, caractérisé en ce que l'on mélange 1 partie en poids d'une solution aqueuse de lactitol présentant une concentration comprise entre 60 et 75 pour cent en poids avec 1 à 3 parties en poids de méthanol ou d'éthanol et en ce que l'on fait alors refroidir le mélange à une température comprise entre 15 et 25 °C tout en agitant et en ce que l'on récupère le monohydrate de lactitol cristallisé.

15. Procédé selon la revendication 14, caractérisé en ce que l'on mélange 1 partie en poids d'une solution de lactitol présentant une concentration comprise entre 65 et 70 pour cent en poids avec 1 à 2 parties en poids de méthanol ou d'éthanol.

16. Procédé selon la revendication 14, caractérisé en ce que l'on mélange 1 partie en poids de la solution de lactitol avec 1 partie en poids d'éthanol et en ce que l'on fait alors refroidir le mélange à une température comprise entre 18 et 22 °C tout en agitant, provoquant la cristallisation du monohydrate de

lactitol et en ce que l'on récupère celui-ci.

17. Procédé selon la revendication 14, caractérisé en ce que l'on mélange 1 partie en poids d'une solution de lactitol présentant une concentration de 70 pour cent en poids avec 1 partie en poids d'éthanol et en ce que l'on fait alors refroidir le mélange à 20 °C tout en agitant, provoquant ainsi la cristallisation du monohydrate de lactitol.

fig. 1.

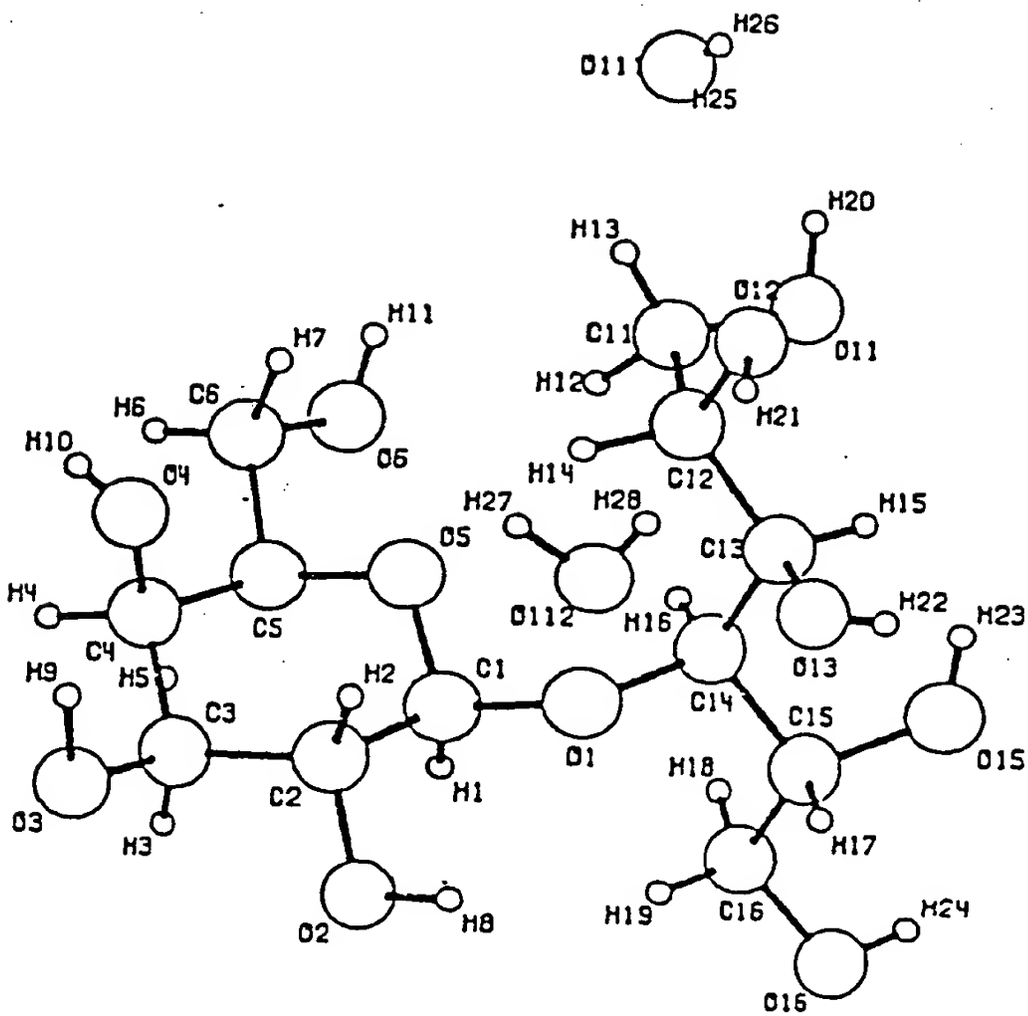
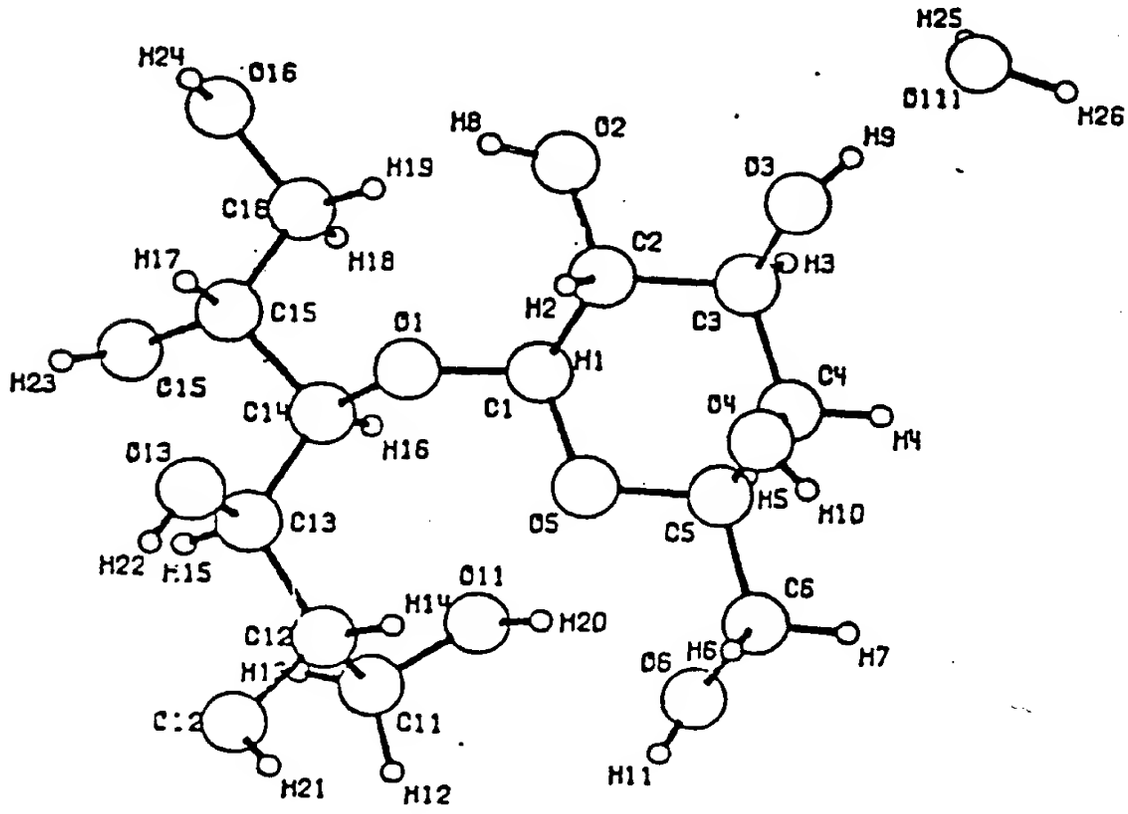

H26
O11
H25
H20
H13
O12
C11
O11
H12
H21
H14
C12
H27
H28
H15
C13
O112
H16
H22
H23
O13
C14
C15
O15
H18
H17
H19
C16
H24
O16
H11
H7
C6
H6
H10
O4
O6
O5
H4
C5
C4
H5
H9
H2
C1
C3
O1
H1
O3
C2
H3
O2
H8

fig.2


H25
O111
H26
H24
O16
H8
O2
H9
O3
H19
C16
C2
H17
H18
H3
C15
H2
O1
C3
H23
C15
H1
C4
C14
C1
O4
H4
H16
O13
H5
H10
C13
O5
C5
H22
H15
O11
C6
H14
C12
H20
H7
O6
H6
H13
C11
H11
H21
H12